



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/891,865	06/25/2001	Giuseppina Bestetti	2901/OJ410	2194

7590 12/11/2003
DARBY & DARBY P.C.
805 Third Avenue
New York, NY 10022

EXAMINER

STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
----------	--------------

1652

DATE MAILED: 12/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/891,865

Applicant(s)

BESTETTI ET AL.

Examiner

David J Steadman

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 31 and 33-60 is/are pending in the application.
- 4a) Of the above claim(s) 49-57 and 60 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 31, 33-42, 44-48, 58 and 59 is/are rejected.
- 7) ☒ Claim(s) 43 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 October 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 062501.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 31 and 33-60 are pending.

Election/Restriction

[2] It should be noted that as written, claim 59 depends from claim 57. However, claim 59 is drawn to a method, while claim 57 is a use claim. Therefore, for purposes of restriction, the examiner grouped claim 59 as though the claim depends from claim 58.

[3] Applicants' election with traverse of Group I, claims 31, 33-48, and 58-59, in the amendment filed September 26, 2003 is acknowledged. Applicants traverse the restriction by arguing that the claims of Invention II (claims 49-57) should be rejoined with the claims of Invention I as the claims of Invention II are drawn to a method of using the product of Invention I. Applicants' argument is not found persuasive.

Applicants' request for rejoinder of the claims of Invention II with the claims of Invention I is acknowledged. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35

Art Unit: 1652

U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. Failure to do so may result in a loss of the right to rejoinder. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. As the product claims of Invention I are not in a condition for allowance, rejoinder is not yet required.

[4] The requirement is still deemed proper and is therefore made FINAL.

[5] Claims 49-57 and 60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

[6] Claims 31, 33-48, and 58-59 are being examined on the merits.

Priority

[7] Applicants claim foreign priority under 35 USC § 119(a)-(d). It is noted that in a previous Office action, the examiner indicated that the foreign priority document had not been filed in the instant application and that applicants state the foreign priority document "will follow". As of the drafting the instant Office action, the foreign priority document has not been received by the Office and applicant has not been granted the benefit of foreign priority as the conditions of 35 USC § 119(a)-(d), particularly 35 USC § 119(b), have not been satisfied.

Oath/Declaration

[8] The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either on an application data sheet or supplemental oath or declaration.

Sequence Compliance

[9] This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences and amino acid sequences in the specification by a proper sequence identifier (see pages 18-21 of the specification). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d).

Specification/Informalities

[10] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Vectors, Host Cells, and Methods for Production of Uridine Phosphorylase and Purine Nucleoside Phosphorylase".

[11] The specification has no "Brief Description of Drawings" section as required by 37 CFR 1.74.

Claim Objections

[12] Claims 39 and 40 are objected to in the recitation of "Tet gene of pBR322" and "kan gene of pET29c". While plasmids pBR322 and pET29c are known in the art, the claims do not identify these as plasmids. It is suggested that, in order to clarify the meaning of the claims, applicants identify pBR322 and pET29c as plasmids (see, e.g., claim 33).

[13] Claim 43 is objected to as the sequences are identified by "SEQ ID NO" and not the proper sequence identifier "SEQ ID NO:". See 37 CFR 1.821(d).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[14] Claim 48 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[15] Claim(s) 33, 35-38, 42, 46-48, is/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 33 is confusing as the claim is drawn to an expression vector having sequences cloned into a pUC18 vector. Ausubel et al. ("Current Protocols in Molecular Biology, John Wiley and Sons, Inc., 1995) teach that an expression vector generally comprises a controllable transcriptional promoter and translational control sequences (page 16.1.1), which are not found within a pUC18 promoter (see GenBank Accession Number L08752) and there is no indication of the presence of a promoter cloned into the claimed vector. Therefore, it is unclear as to how the vector of claim 33 is considered to be an expression vector. It is suggested that applicants clarify the meaning of the claim.

Art Unit: 1652

[b] Claims 35 (claim 36 dependent therefrom) and 37 (claim 38 dependent therefrom) are indefinite in the recitation of "sequence *udp*" and "sequence *deoD*". It is unclear from the claims and the specification as to the intended nucleic acid sequences. It is suggested that, for example, applicants identify their intended sequences by reference to a sequence identifier, i.e., "SEQ ID NO:".

[c] Claims 36 and 38 are indefinite in the recitation of "EMBL sequence having accession number X15689" and "EMBL sequence having accession number M60917". Sequences disclosed in databases such as GenBank or EMBL are frequently updated and the data disclosed therein may be altered. It is suggested that applicants identify the intended sequences by reference to a sequence identifier, i.e., "SEQ ID NO:".

[d] Claim 42 is unclear in the recitation of "aminoacidic units". In the interest of advancing prosecution, the examiner has interpreted the term as "amino acid". It is suggested that applicants replace the term with a term having a clearly identifiable meaning.

[e] Regarding claims 45-46, the phrase "preferably" renders the claims indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

[f] Claim 46 is confusing as it is unclear as to the strain of bacterium to which the claim refers. For purposes of examination, the claim has been interpreted as meaning a strain of *E. coli*. It is suggested that applicant clarify the meaning of the claim.

[g] Claim 47 is confusing as it is unclear as to the expression vector that is present in the claimed host cell. Because claim 47 is dependent upon claim 44, which has the vector of claim 31, it is unclear as to the expression vector present in the host cell of claim 47, i.e., is it the expression vector of claim 31 or the expression vector of claim 41?

[h] Claim 48 provides for the use of host cells, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[16] Claim(s) 31, 33-42, 44-48, and 58-59 is/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim(s) 31 and 33-42 is/are drawn to a recombinant expression vector comprising a genus of genes encoding a mesophilic bacterial uridine phosphorylase enzyme and a genus of genes encoding a mesophilic bacterial purine nucleoside phosphorylase and optionally wherein the mesophilic bacterium is *E. coli* and the gene encoding uridine phosphorylase enzyme is *udp* and the gene encoding purine nucleoside phosphorylase is *deoD*, including naturally and non-naturally occurring genes. Claims 44-47 are drawn to host cells comprising said expression vector. Claims 48 and 58-59 are drawn to methods for producing a genus of polypeptides having uridine phosphorylase and purine nucleoside phosphorylase activities.

The specification fails to provide a sufficient description of the claimed genus of genes as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of

Art Unit: 1652

the genus". Similarly with the claimed genus of genes the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the species encompassed by the genus from others such that one can visualize or recognize the identity of the members of the genus. Given the lack of description, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[17] Claim(s) 31, 33-42, 44-48, and 58-59 is/are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an expression vector comprising the nucleic acid of nucleotides 243-1021 of SEQ ID NO:1 encoding *E. coli* uridine phosphorylase and the nucleic acid of nucleotides 231-960 of SEQ ID NO:3 encoding *E. coli* purine nucleoside phosphorylase, does not reasonably provide enablement for all recombinant expression vector comprising any gene encoding a mesophilic bacterial uridine phosphorylase enzyme and any gene encoding a mesophilic bacterial purine nucleoside phosphorylase and optionally wherein the mesophilic bacterium is *E. coli* and the gene encoding uridine phosphorylase enzyme is *udp* and the gene encoding purine nucleoside phosphorylase is *deoD*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

Art Unit: 1652

- The claims are overly broad in scope: The claims are so broad as to encompass all recombinant expression vector comprising any gene encoding a mesophilic bacterial uridine phosphorylase enzyme and any gene encoding a mesophilic bacterial purine nucleoside phosphorylase and optionally wherein the mesophilic bacterium is *E. coli* and the gene encoding uridine phosphorylase enzyme is *udp* and the gene encoding purine nucleoside phosphorylase is *deoD*. The broad scope of claimed expression vectors is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of genes encoding uridine phosphorylase and purine nucleoside phosphorylase broadly encompassed by the claims. In this case the disclosure is limited to enabling an expression vector comprising the nucleic acid of nucleotides 243-1021 of SEQ ID NO:1 encoding *E. coli* uridine phosphorylase and the nucleic acid of nucleotides 231-960 of SEQ ID NO:3 encoding *E. coli* purine nucleoside phosphorylase polynucleotide.
- The lack of guidance and working examples: The specification provides only a single working example of the recited polynucleotide encoding uridine phosphorylase, i.e., the nucleic acid of nucleotides 243-1021 of SEQ ID NO:1 encoding *E. coli* uridine phosphorylase and provides only a single working example of the recited polynucleotide encoding purine nucleoside phosphorylase, i.e., the nucleic acid of nucleotides 231-960 of SEQ ID NO:3 encoding *E. coli* purine nucleoside phosphorylase. The specification fails to provide guidance regarding isolation or generation of other nucleic acids encoding naturally and non-naturally occurring mesophilic bacterial or *E. coli* uridine phosphorylase and purine nucleoside phosphorylase, which are encompassed by the claims.
- The high degree of unpredictability in the art: In this case, the claims encompass nucleic acids encoding mutant uridine phosphorylases and mutant purine nucleoside phosphorylases. The nucleotide sequence of an encoding nucleic acid determines the corresponding encoded protein's structural and functional properties. Predictability of which changes can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure

Art Unit: 1652

relates to its function. The positions within an encoding nucleic acid's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail above. Thus, a skilled artisan would recognize the high degree of unpredictability that the entire scope of polynucleotides would encode a polypeptide having the desired activity.

- The state of the prior art supports the high degree of unpredictability: The state of the art provides evidence for the high degree of unpredictability in altering a polynucleotide sequence with an expectation that the encoded polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). While it is acknowledged that this reference was published in 1991, to date there remains no certain method for reasonably predicting the effects of even a *single* amino acid mutation on a protein. Such mutations may even completely alter a protein's activity. As a representative example, Witkowski et al. (*Biochemistry* 38:11643-11650) teaches that a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see e.g., Table 1, page 11647). Thus, the prior art acknowledges the unpredictability of altering a protein-encoding sequence with an expectation of obtaining a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a polypeptide.
- The amount of experimentation required is undue: While methods of isolating genes, e.g., by hybridization, or generating variants of a given polynucleotide, e.g., by mutagenesis, are known, it is not

Art Unit: 1652

routine in the art to screen for *all* polynucleotides as encompassed by the instant claims. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

[18] Claim(s) 31, 34-38, 40-42, 44-48, and 58-59 is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Krenitsky et al. (US Patent 4,347,315) in view of Walton et al. (*Nucleic Acids Res* 17:6741; cited in the IDS filed June 25, 2001), Hershfield et al. (*PNAS, USA* 88:7185-7189; cited in the IDS filed June 25, 2001), Bulow et al. (*Trends Biotech* 9:226-231), and Novagen 1997 Catalog.

Claims 31, 34-38, and 44-47 are drawn to a recombinant expression vector comprising a gene encoding a mesophilic bacterial uridine phosphorylase enzyme and a gene encoding a mesophilic bacterial purine nucleoside phosphorylase and host cells comprising said expression vector. Claim 40 limits the vector of claim 31 to having the kanamycin resistance gene of plasmid pET29c. Claims 41-42

Art Unit: 1652

limit the expression vector of claim 31 to a uridine phosphorylase-purine nucleoside phosphorylase gene fusion. Claims 48 and 58-59 are drawn to methods of producing a polypeptide.

Krenitsky et al. teach a method for the preparation of imidazo(4,5-c)pyridine derivatives using an aqueous suspension comprising *E. coli* purine nucleoside phosphorylase and uridine phosphorylase (see Examples 1 and 2). Krenitsky et al. teach that *E. coli* B was found to be an excellent source of the enzymes for practicing their method (column 4, lines 20-24) and that the enzymes are preferably purified (column 4, lines 41-43). Krenitsky et al. do not teach an expression vector comprising genes encoding mesophilic bacterial uridine phosphorylase and purine nucleoside phosphorylase, host cells containing said expression vector, and a method for producing a protein using said expression vector as encompassed by the claims.

Walton et al. teach the nucleic acid sequence of the *E. coli* *udp* gene encoding uridine phosphorylase.

Hershfield et al. teach the nucleic acid sequence of the *E. coli* *deoD* gene encoding purine nucleoside phosphorylase (page 7186).

Bulow et al. teach recombinantly fusing enzyme-encoding nucleic acids to produce a bifunctional fusion enzyme with the component enzymes attached via a peptide linker (page 230, left column, top) and a method for preparation thereof (page 227). Bulow et al. teach numerous advantages of fusion enzymes including proximity effects (page 226, right column, bottom to page 227, left column, top and page 231, right column, top) and ease of purification requiring the purification of only a single fusion enzyme instead of two separate enzymes (page 231, left column, middle). Bulow et al. acknowledge that the preparation and use of such fusion enzymes is well known in the art by disclosing "[o]ver the years, a variety of artificial bifunctional enzymes have been prepared by gene fusion *in vitro*" (page 227, right column, bottom).

Novagen 1997 Catalog teaches expression plasmid pET29c comprising a kanamycin resistance selectable marker (page 156). Novagen 1997 Catalog teaches numerous advantages of using this vector for protein expression (page 42, left) and assert that their expression system is "the most powerful system yet developed for the cloning and expression of recombinant proteins in *E. coli*" (page 42, right, top).

Art Unit: 1652

Novagen 1997 Catalog teaches that particular strains of *E. coli* K12 can be used in their expression system including HMS174 and NovaBlue (page 43, top).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Krenitsky et al., Walton et al., Hershfield et al., Bulow et al., and Novagen 1997 Catalog to generate a uridine phosphorylase-purine nucleoside phosphorylase fusion enzyme fused directly or via a peptide linker by appropriately inserting nucleic acids encoding *E. coli* uridine phosphorylase and purine nucleoside phosphorylase into plasmid pET29c followed by transformation of competent *E. coli* followed by expression and purification of the encoded fusion enzyme for use in the method of Krenitsky et al. One would have been motivated to express and purify a uridine phosphorylase-purine nucleoside phosphorylase fusion enzyme for use in the method of Krenitsky et al. because of the advantages of fusion enzymes in an enzymatic reaction as taught by Bulow et al., e.g., proximity effects and one step purification instead of purifying individual enzymes. One would have a reasonable expectation of success for generating a uridine phosphorylase-purine nucleoside phosphorylase fusion enzyme fused via a peptide linker by appropriately inserting nucleic acids encoding *E. coli* uridine phosphorylase and purine nucleoside phosphorylase into plasmid pET29c followed by transformation of competent *E. coli* followed by expression and purification of the encoded fusion enzyme for use in the method of Krenitsky et al. because of the results of Krenitsky et al., Walton et al., Hershfield et al., Bulow et al., and Novagen 1997 Catalog. Therefore, claims 31, 34-38, 40-42, 44-45, 46-48, and 58-59, drawn to the expression vector, host cells, and method for producing a protein as described above would have been obvious to one of ordinary skill in the art.

[19] Claim(s) 31, 34-39, 41-42, 44-45, and 47-48 is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Krenitsky et al. (US Patent 4,347,315) in view of Walton et al. (*Nucleic Acids Res* 17:6741; cited in the IDS filed June 25, 2001), Hershfield et al. (*PNAS, USA* 88:7185-7189; cited in the IDS filed June 25, 2001), Bulow et al. (*Trends Biotech* 9:226-231), and Sambrook et al. ("Molecular Cloning, A Laboratory Manual, Second Edition", Cold Spring Harbor Press, 1989).

Art Unit: 1652

Claims 31, 34-38, 41-42, 44-45, and 47-48 31 are drawn to a recombinant expression vector, host cells, and a method for producing a protein as described above. Claim 39 limits the tetracycline resistance gene to the Tet gene of pBR322.

Krenitsky et al., Walton et al., Hershfield et al., and Bulow et al. disclose the teachings as described above. Krenitsky et al. do not teach an expression vector comprising genes encoding mesophilic bacterial uridine phosphorylase and purine nucleoside phosphorylase, host cells containing said expression vector, and a method for producing a protein using said expression vector as encompassed by the claims.

Sambrook et al. teach selectable markers encoded by a plasmid are used to select for those clones comprising the plasmid (page 1.5). Sambrook et al. teach tetracycline is one of the most commonly used selectable markers (page 1.5) and further disclose, "[v]irtually all plasmid vectors in common use carry one or more of the antibiotic resistance genes described above" including tetracycline (page 1.6).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Krenitsky et al., Walton et al., Hershfield et al., Bulow et al., and Sambrook et al. to generate a uridine phosphorylase-purine nucleoside phosphorylase fusion enzyme fused directly or via a peptide linker by appropriately inserting nucleic acids encoding *E. coli* uridine phosphorylase and purine nucleoside phosphorylase into an expression plasmid comprising a tetracycline resistance gene followed by transformation of competent *E. coli* and expression and purification of the encoded fusion enzyme for use in the method of Krenitsky et al. One would have been motivated to express and purify a uridine phosphorylase-purine nucleoside phosphorylase fusion enzyme for use in the method of Krenitsky et al. because of the advantages of fusion enzymes in an enzymatic reaction as taught by Bulow et al., e.g., proximity effects and one step purification instead of purifying individual enzymes. One would have motivated to use an expression vector comprising a tetracycline resistance gene because of its common and established use as a selectable marker as described by Sambrook et al. above. One would have a reasonable expectation of success for generating a uridine phosphorylase-purine nucleoside phosphorylase fusion enzyme fused via a peptide linker by appropriately inserting nucleic acids encoding

Art Unit: 1652

E. coli uridine phosphorylase and purine nucleoside phosphorylase into an expression plasmid comprising a tetracycline resistance gene followed by transformation of competent *E. coli* and expression and purification of the encoded fusion enzyme for use in the method of Krenitsky et al. because of the results of Krenitsky et al., Walton et al., Hershfield et al., Bulow et al., and Sambrook et al. Therefore, claims 31, 34-39, 41-42, 44-45, and 47-48, drawn to the expression vector, host cells, and method for producing a protein as described above would have been obvious to one of ordinary skill in the art.

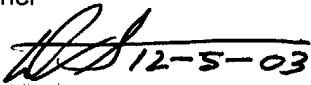
Conclusion

[20] Status of the claims:

- Claims 31 and 33-60 are pending.
- Claims 49-57 and 60 are withdrawn from consideration.
- Claims 31, 33-42, 44-48, and 58-59 are rejected.
- Claim 43 would be allowable if rewritten to overcome the objection set forth in this Office action.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652


DAVID STEADMAN
PATENT EXAMINER